REMARKS

Claims 19, 20, 25-27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50, and 52-61 are pending in this application.

Although the Examiner has rejected all of the pending claims under 35 U.S.C. §102 and the enablement requirement of 35 U.S.C. § 112, first paragraph, the Examiner has stated that the instant application and priority Application Nos. 60/181,684 and 60/183,356 enable "pharmaceutical compositions comprising the 1-51 and 1-52 fragments of SEQ ID NO:1." Final Office Action of June 1, 2007, at 6 and 7. Moreover, because Application Nos. 60/181,684 and 60/183,356 antedate the art of record, the Examiner concludes that "[c]laims limited to residues 1-51 or 1-52 of SEQ ID NO:1 are allowable over the prior art of record." Id., at 8.

However, the Examiner contends that the instant application (and, accordingly, the priority applications) do not enable claims relating to (1) amino acids 8-41 or (2) 95% variants of any portion of SEQ ID NO:1. The Examiner's denial of priority to Application Nos. 60/181,684 and 60/183,356 is based on this same alleged lack of enablement. Because the Examiner's enablement argument draws no distinction between the instant application and those two priority applications, it follows that if the instant application enables amino acids 8-41 and 95% variants, Applicants are entitled to priority to at least Application Nos. 60/181,684 and 60/183,356. In turn, since those provisional applications were filed before the effective dates of the cited art, priority to those applications renders the novelty rejection moot. Thus, if Applicants demonstrate

that the instant application enables amino acids 8-41 and 95% variants, the pending claims should be allowable[1].

Applicants maintain that the instant application and each of priority applications 60/181,684 and 60/183,356 do enable amino acids 8-41 and 95% variants of amino acids 1-51 of SEQ ID NO:1 that bind to BAFF. Since Applicants have already presented extended arguments on both points in previous filings, Applicants only summarize those earlier arguments before presenting new remarks.

Applicants have enabled 95% identical sequence variants

Applicants have previously argued that the Examiner's reliance on the supposed inability of the skilled artisan to predict which 95% variants will retain BAFF-binding activity is misplaced. Under In re Angstadt, the test for enablement is not whether experimentation would be required for the skilled artisan to make and use the claimed invention, but whether any such experimentation would be undue. 537 F.2d 498 (CCPA 1976). Indeed, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988)." Although the level of predictability in the art to which the invention relates is one of the eight factors in the undue experimentation analysis under In re Wands, the Federal Circuit has explicitly rejected

[1] Since Application Nos. 60/181,684 and 60/183,356 antedate the art of record, the Examiner need not decide Applicants' claim to priority to Application No. 60/149,378. However, for the reasons provided in their previous replies, Applicants maintain for the record that they are entitled to priority to Application No. 60/149,378.

the notion that the skilled artisan must be able to predict with reasonable certainty which experiments will yield the claimed product:

> "If . . . the disclosure must provide 'guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction, whether the claimed product will be obtained,' as the dissent claims, then all 'experimentation' is 'undue', since the term 'experimentation' implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act." In re Angstadt, 537 F.2d at 503 (emphasis in the original).[2]

Applicants have provided a wealth of evidence that, under the proper test, the specification fully enables 95% variants that bind to BAFF. The skilled artisan could not only make and use the claimed invention without undue experimentation, but could in fact predict many variants likely to retain activity. As discussed in greater detail in previous submissions, Bowie et al. (previously provided) teaches that a systematic approach (with no specific guidance as to which residues are critical for BCMA activity) would be expected to yield a high fraction of functional variants. Moreover, both the human and mouse BCMA sequences were known in the art. Madry et al. (previously provided). The skilled artisan would know that a comparison of these homologues would provide considerable predictability: conserved residues are likely to be important for activity, but substituting non-conserved residues for the corresponding amino acid in the mouse sequence (or even other amino acids) will likely preserve activity.

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[2] The Examiner's attempt to distinguish the facts of In re Angstadt and In re Wands is inapposite. These are two leading cases on enablement in the chemical and biological arts. Applicants do not cite them for their particular fact patterns, but for their general articulation of the enablement standard. Nothing in the internal logic of the opinions themselves or their subsequent application by the courts suggests that the principles articulated in these cases are limited to their particular facts.

A recent precedential opinion of the Board of Patent Appeals and Interferences powerfully supports Applicants' position that the specification and the priority documents enable 95% variants that bind BAFF. In Ex parte Kubin, the Board reversed the Examiner's enablement rejection of claims relating to polypeptides "(1) which are 'at least 80% identical to amino acids 22-221 of SEQ ID NO:2' (the amino acid sequence for the extracellular domain of NAIL without the signal sequence) and (2) which bind to CD48." 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007).

The Board found that the specification did not disclose any of the following: (1) "any variants" (Finding of Fact # 22); (2) "which 20% of amino acid residues should be changed in order to maintain the biological functions for binding to CD48" (Finding of Fact # 23); or (3) "a correlation between function (binding to CD48) and structure responsible for binding to CD48 (other than the entire extracellular domain)" (Finding of Fact # 25). The Board also found that molecular biology at the time of filing was generally an unpredictable art (Finding of Fact # 26) and that "the experimentation involved to produce other sequences within the scope of the claims and thus to practice the full scope of claim 73, would have been well within the skill of those in the art and thus would have been routine" (Finding of Fact # 29). Id. at 1415-16. The Board concluded that the specification enabled the full scope of the claim, stating that "[t]he amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The necessary techniques to do so were well known to those skilled in the art." Id. at 1416 (citations omitted).

If the 80% variants at issue in Kubin are enabled, there can be no question about enablement of Applicants' pending claims. Any experimentation needed to produce the

claimed polypeptides would be even more routine than that required to practice the Kubin invention. Here, the claims require 95% identity to a 51 amino acid polypeptide, and are thus of far narrower scope than Kubin's 80% variants of a 200 amino acid polypeptide. Moreover, whereas Kubin provided no correlation between structure and function, the skilled artisan seeking to practice Applicants' invention would know to compare the human and mouse BCMA sequences for guidance as to those residues that are likely (and those that are unlikely) to be important for BAFF-binding activity.[3] Accordingly, the Examiner's conclusion that Applicants' specification and priority applications do not enable the claimed invention is inconsistent with the clear holding of the Board in Kubin.

In view of the foregoing remarks, Applicants respectfully request that the rejection of the claims for lack of enablement of 95% variants that bind to BAFF be reconsidered and withdrawn.

Applicants have enabled amino acids 8-41 of SEQ ID NO:1

Applicants have previously argued that the Examiner has not met the Office's burden for establishing lack of enablement of amino acids 8-41. Applicants are entitled to a presumption of enablement; the Examiner bears the burden of giving reasons, supported by the record as a whole, why undue experimentation would be necessary for

[3] The Board did find that the Kubin specification taught how to (1) make variants of the recited sequences, (2) calculate the percent identity between the recited sequences and the variants, and (3) test the variant sequence to determine binding activity (Finding of Fact # 24). Kubin at 1416. However, Applicants' specification contains the same teachings for the claimed invention at pages 15, 8, and 23-36, respectively.

the skilled artisan to make and use the claimed invention. In re Angstadt, 537 F.2d 498 (CCPA 1976). The Examiner returns again and again to the fact that the application does not describe an actual reduction to practice of an active BCMA fragment consisting of amino acids 8-41 of SEQ ID NO:1[4]. However, Federal Circuit case law and the M.P.E.P. make explicitly clear that working examples are not required. See M.P.E.P. § 2164.02 ("Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed."); see also Applicants' Reply of March 28, 2007, at 23-24 (discussing In re Strahilevitz, 668 F.2d 1229, 1232 (Fed. Cir. 1982) and Gould v. Quigg, 822 F. 2d 1074, 1078 (Fed. Cir. 1987)). Thus, the mere fact that the application does not include a working example of a BCMA fragment consisting of amino acids 8-41 can not be sufficient to meet the Examiner's burden.

Even if the Office had met its burden under In re Angstadt (and Applicants maintain it has not), Applicants have rebutted the Examiner's position. Although the mere absence of a working example placed no burden on Applicants to provide evidence of enablement, Applicants brought the Examiner's attention to the specification's disclosure that amino acids 8-41 are the "cysteine-rich domain" (CRD) of BCMA and to Smith et al. (previously provided), which teaches that the CRD is the "canonical motif" of this family of receptors.

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[4] Applicants note that the specification does provide a working example within the scope of the nearly all of the claims at issue here. As discussed at length in previous submisions, Applicants actually reduced to practice a BCMA-Ig fusion comprising amino acids 1-51 of SEQ ID NO:1. This polypeptide obviously falls within the scope of sequences comprising amino acids 8-41 of SEQ ID NO:1 or variants thereof.

The Examiner's previous response to this evidence (Office Action of September 29, 2006, at 6-7), which consisted solely of attacking the relevance of Smith et al., is doubly ineffective. First, the Examiner's argument against Smith's relevance is legally inadequate. Applicants bear no burden to prove enablement; they volunteered Smith et al. solely in the interests of advancing prosecution. Thus, even if the Examiner had shown that Smith et al. provides no support whatsoever for enablement, the burden would remain with the Examiner to overcome Applicants' presumption of enablement. Second, the Examiner's comments regarding Smith are simply inaccurate on the scientific and textual facts. See Applicants' Reply of March 28, 2007, at 24-26.

Still bearing no burden to prove enablement, Applicants also presented Liu et al., a post-filing publication describing the crystal structure of "TALL-1" (i.e., BAFF) bound to "eBCMA" (amino acids 5-43). Liu et al. lists 9 amino acids in BCMA that are directly involved in the BCMA:BAFF interaction and another 6 amino acids in BCMA that form disulfide bridges; all 15 of these amino acid positions lie within amino acids 8-41 of SEQ ID NO:1. Liu et al. thus provides dramatic evidence that amino acids 8-41 of SEQ ID NO:1 are likely sufficient for BAFF binding activity. See Applicants' Reply of March 28, 2007, at 26-27.

The outstanding Final Office Action provides no answer to any of the arguments summarized above. The Examiner merely sounds again the tired refrain that the specification does not provide "evidence of efficacy or binding of the peptide 8-41 of SEQ ID NO:1 of SEQ ID NO:1 to SEQ ID NO:9 [BAFF]," i.e., the specification lacks a working example proving that amino acids 8-41 are sufficient for BAFF-binding. Final Office Action of June 14, 2007, at 4. The Examiner does not respond to Applicants'

arguments that neither the absence of a working example nor the asserted irrelevance of Smith et al. is legally sufficient to meet the Office's burden. Similarly, the Examiner apparently has no answers to the powerful evidence for enablement provided the BCMA:BAFF structure of Liu et al. or to the charge that the Examiner's comments regarding Smith et al. are simply wrong on the facts.

In light of the arguments summarized here and the Examiner's utter failure to respond to them, Applicants respectfully request that the rejection of the claims for alleged lack of enablement of amino acids 8-41 be withdrawn.

Conclusion

In view of the foregoing remarks, Applicants respectfully submit that all outstanding rejections have been overcome. Accordingly, reconsideration of claims and expedited allowance are earnestly requested. The Examiner is urged to call the undersigned with any questions at (617) 452-1669.

Applicants believe that any fee required for the entry of this amendment is accounted for by the accompanying Petition for Extension of Time. However, in the event of an error, please grant any additional extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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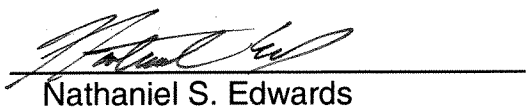
Dated: October 31, 2007

By: 
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